REMARKS

Claims 1-3, 5, 7, 9-16, 22-23, 25, and 26 are pending in the above-identified application. Claims 1-3, 5, 7, 9-16, and 22-23 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1-3, 5, 7, 9-16, 22-23, and 25 stand rejected under 35 U.S.C. §§ 102(b) and 103(a) as allegedly anticipated by or, in the alternative, obvious over Simkiss *et al.* (WO 94/02412). Claim 26 stands rejected as allegedly obvious over Simkiss *et al.* (WO 94/02412) in view of Gerhart *et al.* (U.S. Patent No. 4,843,112). Claims 1-3, 5, 7, 9-16, 22-23, and 26 also stand rejected under the judicially created doctrine of obviousness-type double patenting. With this response, Claims 2, 5, 22-23, and 26 have been cancelled, and Claims 1, 3, 7, 9-16, and 25 have been amended. Favorable reconsideration and allowance of the pending claims are requested.

I. Applicants' Invention

In one aspect, the present invention is directed to a method of treating a bone defect using a strongly bioresorbable, synthetic poorly crystalline apatitic (PCA) calcium phosphate. The poorly crystalline apatitic calcium phosphate has a calcium to phosphate molar ratio in the range of about 1.2 to 1.68 and further has the X-ray diffraction pattern of naturally occurring bone. Upon implantation at an implant site requiring bone growth, the poorly crystalline apatitic calcium phosphate is resorbed, and bone is formed at the implant site.

In another aspect, the present invention is directed to a method of embedding a prosthetic device using a paste comprising an amorphous calcium phosphate, an acidic second calcium phosphate, and a physiologically acceptable fluid in an amount sufficient to provide a paste of formable or injectable consistency. The paste is converted *in vivo* to a hardened calcium

phosphate product in an endothermic process. The hardened calcium phosphate is resorbed and replaced with bone.

II. Claim Amendments

Claim 1 has been amended to specify that the poorly crystalline apatitic calcium phosphate is implanted at an implant site requiring bone growth. Support for this amendment is found throughout the specification, for example at page 11, lines 3 to 27. Claim 1 has also been amended to recite that the calcium to phosphate ratio is a molar ratio. Support for this amendment is found at page 20, line 23 through page 21, line 2. All other amendments to Claim 1 are amendments in form only and, correspondingly, do not introduce new matter.

Claims 3, 7, 9-16, and 25 have been amended for clarification, as well as to correct typographical errors and claim dependencies. None of these amendments introduces new matter.

III. The Indefiniteness Rejections

Claims 1, 3, 7, 9, and 10-16 have been rejected as allegedly indefinite for failing to specify the units of the calcium to phosphate ratio. Claim 1 has been amended to recite that the calcium to phosphate ratio is a molar ratio.

Claims 1, 3, 7, 9, and 10-16 have also been rejected as allegedly indefinite because the term "similar" in the phrase "characterized by an X-ray diffraction pattern similar to naturally occurring bone" encompasses elements not disclosed in the claims. Claim 1 has been amended to recite that the poorly crystalline apatitic calcium phosphate has "the X-ray diffraction pattern of naturally occurring bone," thereby eliminating the language to which the Examiner objected.

Claims 2, 5, 10-16, and 22-23 have been rejected on the grounds that the phrase "identifying a bone site suitable for receiving an implant" is allegedly indefinite because the

claims do not specify the requirements for identifying such a site. With this response, Claim 2 and its dependents have been cancelled, thereby rendering this rejection moot.

Claims 2, 5, 10-16, 22-23, and 25 have been rejected on the grounds that the phrase "associated with an endothermic reaction" is allegedly indefinite because the claims do not specify the manner in which the hardening process of the paste is associated with the endothermic reaction. Claim 25 has been amended to specify that the paste is converted at the implant site to a hardened calcium phosphate product "in an endothermic process," thereby clarifying this relationship.

For the foregoing reasons, Applicants submit that the indefiniteness rejections have been overcome.

IV. The Anticipation and Obviousness Rejections

Claims 1-3, 5, 7, 9-16, 22-23, and 25 have been rejected as allegedly anticipated by or, in the alternative, obvious over Simkiss *et al.* (WO 94/02412). Claims 1, 3, 7, 9-16, and 25 remain pending after entry of this Amendment. These claims fall into two groups: (1) those directed to a method of treating a bone defect using a poorly crystalline apatitic calcium phosphate (Claims 1, 3, 7, and 9-16) and (2) those directed to a method of embedding a prosthetic device (Claim 25). The relevance of Simkiss *et al.* to each of these groups of claims is addressed separately below.

Claims 1, 3, 7, and 9-16

Simkiss *et al.* teach a precursor material comprising an amorphous composition containing calcium and phosphate ions, as well as inhibitor components, such as magnesium and/or pyrophosphate ions (page 2, lines 33-37). The amorphous precursor material is applied to a bone defect site *in vivo*, where the inhibitor is leached from the precursor material and the material is transformed to crystalline hydroxyapatite (page 3, lines 2-14 and page 4, line 37

through page 5, line 8). Simkiss *et al.*, therefore, teach a method of repairing a bone defect using a composition including an amorphous calcium phosphate and a crystallization inhibitor.

In contrast, Claims 1, 3, 7, and 9-16 are directed to a method of treating a bone defect by implanting a poorly crystalline apatitic calcium phosphate at an implant site requiring bone growth. Thus, the Simkiss method and the claimed invention are directed to two different processes. The Simkiss method introduces an amorphous calcium phosphate into an implant site and promotes further reaction of the amorphous calcium phosphate to form a crystalline hydroxyapatite. The claimed method instead calls for introducing an apatitic calcium phosphate of low crystallinity; no further reaction of the implant material occurs. An amorphous calcium phosphate and a poorly crystalline apatitic calcium phosphate differ in both chemical composition and degree of crystallinity. On this basis alone, Applicants' claimed method of treating a bone defect is clearly novel over Simkiss *et al.*

Further, Simkiss *et al.* nowhere suggest implanting a poorly crystalline apatitic calcium phosphate having the bioresorption properties set forth in Claims 1, 3, 7, and 9-16. Simkiss *et al.* clearly require contact of an amorphous calcium phosphate with physiological saline to initiate the reaction, a requirement suggestive of an *in vivo* process. Simkiss *et al.* additionally teach that the transformation of the amorphous material is desirably slow so as to allow the developing bone mineral to integrate into normal healing processes (page 3, lines 17-20), which is also suggestive of an *in vivo* process. There is simply no passage in Simkiss *et al.* suggesting *ex vivo* manufacture of a highly resorbable, poorly crystalline apatitic calcium phosphate and its use as an implant material. Therefore, Applicants' claimed method is not obvious in view of Simkiss *et al.*

Accordingly, Applicants submit that the method of Claims 1, 3, 7, and 9-16 has been distinguished over Simkiss *et al.* and the Section 102(b) and Section 103(a) rejections of these claims have been overcome.

Claim 25

In addition to the teachings discussed above, Simkiss *et al.* provide that their amorphous precursor material may be used to assist in the attachment of prostheses (page 6, lines 1-2). Specifically, Simkiss *et al.* state that

> [a] mixture of fast-setting and slow-setting compositions of the invention will encourage vascularisation of an adhesive material such as a poly methyl methacrylate cement and made [sic] such mixtures suitable for coating the contact area of implanted bone prostheses

(page 6, lines 27-32). In this vague passage, Simkiss *et al.* appear to be suggesting the attachment of bone prostheses using a combination of amorphous calcium phosphate and an additional adhesive material.

Amended Claim 25, however, is directed to a method of embedding a prosthetic device by applying a paste to the surface of the prosthesis, wherein the paste comprises an amorphous calcium phosphate, an acidic second calcium phosphate, and a physiologically acceptable fluid in an amount sufficient to provide a paste of formable or injectable consistency. This paste hardens at the implant site in an endothermic process, fixing the prosthesis in place. The hardened calcium phosphate is ultimately resorbed and replaced with bone. Thus, in contrast to the teachings in Simkiss *et al.*, Applicants' claimed method requires an amorphous calcium phosphate and an acidic calcium phosphate, functioning in a hardening reaction, to secure prostheses *in vivo*. The Simkiss material is not capable of hardening on its own, as evidenced by the use of an additional adhesive material to secure the prostheses. The claimed method is,

therefore, novel over Simkiss *et al.* Further, because Simkiss *et al.* entirely lacks any meaningful suggestion that their amorphous calcium phosphate materials are alone sufficient to secure prostheses, Simkiss *et al.* cannot render the claimed method obvious.

Moreover, the method of Claim 25 may be independently distinguished from Simkiss *et al.* on other grounds. In Claim 25, Applicants specify that their paste comprises an amorphous calcium phosphate and an acidic second calcium phosphate. This disclosure is in sharp contrast to the teaching in Simkiss *et al.* that "it is possible to mix several amorphous calcium phosphates chosen to have different rates of transformation" (page 6, lines 12-15) and that a "mixture of fast-setting and slow-setting compositions" may be used to attach a prosthesis (page 6, lines 27-32). Such broad and vague teachings cannot anticipate Applicants' claim to the use of a specified paste composition for embedding a prosthetic device. Moreover, there is absolutely no suggestion in Simkiss *et al.* that an additional acidic calcium phosphate would be a desirable component of an adhesive composition. Simkiss *et al.* is, therefore, insufficient to sustain the Section 103(a) rejection of Claim 25.

Accordingly, Applicants submit that the method of Claim 25 has been distinguished over Simkiss *et al.* and that the Section 102(b) and Section 103(a) rejections of this claim have been overcome.

Finally, Applicants note that Claim 26 has been rejected as allegedly obvious over Simkiss *et al.* (WO 94/02412) in view of Gerhart *et al.* (U.S. Patent No. 4,843,112). Without acquiescing in the propriety of this rejection, Applicants have cancelled Claim 26, thereby rendering this objection moot.

V. The Double Patenting Rejections

Claims 1-3, 5, 7, 9-16, 22-23, and 26 have been rejected under the judicially created doctrine of obviousness-type double patenting. Claims 1-3, 5, 7, 9-16, 22-23, and 26 are allegedly unpatentable over claims 13-27 of United States Patent No. 6,287,341. Claims 1-3, 5, 7, 9-16, and 22-23 are allegedly unpatentable over Claims 1-14 of United States Patent No. 6,214,368, Claims 1-2 of United States Patent No. 6,132,463, Claims 1-21 of United States Patent No. 6,027,742, and Claims 1-9 of United States Patent No. 6,331,312. In the event the pending claims are found to be otherwise allowable, Applicants will consider the appropriateness of filing a terminal disclaimer to overcome this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, it is submitted that Claims 1, 3, 7, 9-16, and 25 are in condition for allowance, which action is earnestly solicited. The Examiner is invited to contact the undersigned by telephone should any issues remain outstanding.

A Petition for a three-month extension of time, extending the period for response up to and including December 18, 2002, is included with this Amendment and Reply, as is an authorization to charge our Deposit Account No. 08-0219 the associated fee of $460.00 pursuant to 37 C.F.R. § 1.17(a)(3). No additional fees are believed due. However, in the event that any fees are due in connection with this application, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 08-0219.

Respectfully submitted,

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MARKED-UP COPY OF AMENDED CLAIMS

1. A method for treating a bone defect, comprising:

[~~identifying a bone site suitable for receiving an implant; and introducing~~]

providing a strongly resorbable, synthetic poorly crystalline apatitic (PCA) calcium phosphate [~~at the implant site~~], the [~~PCA~~] poorly crystalline apatitic calcium phosphate [~~have~~] having a calcium to phosphate [~~ratio~~] (Ca:P) molar ratio in the range of about 1.2 [-] to 1.68 and [~~characterized by an~~] further having the X-ray diffraction pattern [~~similar to~~] of naturally occurring bone [~~and substantially~~], as shown in Figure 3c, and

implanting the poorly crystalline apatitic calcium phosphate at an implant site requiring bone growth, whereby the implanted [~~PCA~~] poorly crystalline apatitic calcium phosphate is resorbed with a resorption rate characterized in that, when placed in a rat intramuscular site, at least 1 g of the [~~PCA~~] poorly crystalline apatitic calcium phosphate is at least 80% resorbed within one year, and bone is formed at the implant site.

3. The method of claim 1, wherein the poorly crystalline apatitic calcium phosphate is [~~introduced~~] implanted in the form selected from the group consisting of paste, putty and preshaped object.

7. The method of claim 1, wherein the [~~strongly bioresorbable,~~] poorly crystalline apatitic calcium phosphate has an X-ray diffraction pattern comprising broad peaks at 2θ values of 26°, 28.5°, 32°, and 33°.

9. The method of claim 1, wherein the [~~strongly bioresorbable,~~] poorly crystalline apatitic calcium phosphate is characterized in that, when placed in a rat intramuscular site,

[~~resorption of~~] at least 1 g of the [~~material~~] poorly crystalline apatitic calcium phosphate is at least 80% resorbed within one month.

10. The method of claim 1 [~~or 2~~], wherein the implant site comprises a tooth socket.

11. The method of claim 1 [~~or 2~~], wherein the implant site comprises a non-union bone.

12. The method of claim 1 [~~or 2~~], wherein the implant site comprises a bone prosthesis.

13. The method of claim 1 [~~or 2~~], wherein the implant site comprises an osteoporotic bone.

14. The method of claim 1 [~~or 2~~], wherein the implant site comprises an intervertebral space.

15. The method of claim 1 [~~or 2~~], wherein the implant site comprises an alveolar ridge.

16. The method of claim 1 [~~or 2~~], wherein the implant site comprises a bone fracture.

25. A method for embedding a prosthetic device, comprising:

introducing a prosthesis at an implant site;

applying a paste to a surface of the prosthesis, the paste comprising an amorphous calcium phosphate [~~and~~], an acidic second calcium phosphate, and a physiologically acceptable

fluid [~~of~~] in an amount sufficient to provide a paste of formable or injectable consistency, whereby the paste is converted at the implant site to a hardened calcium phosphate product in [~~a hardening process associated with an endothermic reaction~~] an endothermic process; and

allowing the hardened calcium phosphate to be resorbed and replaced thereby with bone.